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REVIEWS: CURRENT TOPICS

Dietary polyphenols and mechanisms of osteoarthritis☆,☆☆

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Abstract

Osteoarthritis is a condition caused in part by injury, loss of cartilage structure and function, and an imbalance in inflammatory and anti-inflammatory pathways. It primarily affects the articular cartilage and subchondral bone of synovial joints and results in joint failure, leading to pain upon weight bearing including walking and standing. There is no cure for osteoarthritis, as it is very difficult to restore the cartilage once it is destroyed. The goals of treatment are to relieve pain, maintain or improve joint mobility, increase the strength of the joints and minimize the disabling effects of the disease. Recent studies have shown an association between dietary polyphenols and the prevention of osteoarthritis-related musculoskeletal inflammation. This review discusses the effects of commonly consumed polyphenols, including curcumin, epigallocatechin gallate and green tea extract, resveratrol, nobiletin and citrus fruits, pomegranate, as well as genistein and soy protein, on osteoarthritis with an emphasis on molecular antiosteoarthritic mechanisms.

Keywords: Polyphenols; Antioxidant; Inflammation; Pain management; Osteoarthritis; Molecular mechanism

1. Introduction

Osteoarthritis (OA) is the most frequent musculoskeletal disorder and the most common degenerative joint disease in the elderly [1]. OA is a major cause of morbidity, disability and loss of function particularly in the aging population [1], and it is considered as the most consequential rheumatic condition in terms of social–economic impacts [2,3].

OA is a condition caused in part by injury, loss of cartilage structure and function, and a dysregulation of proinflammatory and anti-inflammatory pathways [4,5]. OA primarily affects the articular cartilage and subchondral bone of synovial joints, and results in joint failure, leading to pain with weight bearing activity including walking and standing [6]. The symptoms of OA include pain, stiffness in the morning, joint swelling, limited range of motion, decreased physical function, restriction of social activities and/or compromised work capacity [7]. The intervention that provides for reduced pain, inflammation and/or stiffness associated with OA can help improve the joint mobility of patients with OA.

Chondrocytes are the cells found in hyaline cartilage, a flexible connective tissue located in the joints between bones [8]. Chondrocytes produce and maintain the cartilaginous matrix, which is a large amount of extracellular matrix composed of type II collagen fibers, abundant ground substance rich in proteoglycan (PG) and elastin

Abbreviations: ADAMTS, a disintegrin and metalloproteinase with thrombospondin motifs; AGE, advanced glycation end products; AP-1, activator protein-1; COX-2, cyclooxygenase-2; EGCG, epigallocatechin gallate; ERK, extracellular signal-regulated kinases; GAG, glycosaminoglycans; IL, interleukin; iNOS, inducible nitric oxide synthase; JAK/STAT, janus kinase-signal transducer and activator of transcription; JNK, c-Jun-N-terminal kinases; MAPK, mitogen activated protein kinases; MKK-3, MAPK kinase-3; MMP, matrix metalloproteinases; NF-κB, nuclear factor kappa-B; NO, nitric oxide; OA, osteoarthritis; PARP, poly (ACP-ribose) polymerase; PG, proteoglycan; PGE_2, prostaglandin E_2; PMF, polymethoxylated flavones; ROS, reactive oxygen species; TGF, transforming growth factor; TIMP-1, tissue inhibitor of metalloproteinase 1; TNF, tumor necrosis factor; WOMAC, Western Ontario and McMaster Universities.

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fibers [8]. Proinflammatory cytokines [e.g., interleukin (IL)-1β, IL-6 and tumor necrosis factor (TNF)-α] have been shown to modulate extracellular matrix turnover, to accelerate the degradation of cartilage and to induce chondrocyte apoptosis in the development of OA [5,6,9,10].

Although the etiology and underlying mechanism of OA are complicated, a body of evidence suggests that the progression of OA in patients may be primarily driven by an increase in oxidative stress [11]. Nitric oxide (NO) and its redox derivatives have been shown to be involved in cartilage damage [12], and the reactive oxygen species (ROS) scavenger superoxide dismutase is reduced in the cartilage of humans and animal models of OA [13]. ROS production has been found to increase in joint diseases such as OA and rheumatoid arthritis [14]. They are involved in both normal chondrocyte activity and the cartilage damage associated with OA [15].

It was postulated that in OA cartilage, there is an imbalance between (a) anabolic synthesis or repair of matrix components by growth factors [16–18] and (b) catabolic breakdown of matrix by inflammatory cytokines (i.e., IL-1β); matrix metalloproteinase (MMP)-1, -3 or -13; a disintegrin and metalloprotease with thrombospondin motifs (ADAMTS)-4 and -5 (also called aggrecanases); cyclooxygenase (COX)-2 expression and prostaglandins [i.e., prostaglandin E_2 (PGE_2)]; and proteases [5,10,18–21]. These inflammatory cytokines and proteases act to perpetuate inflammation while contributing to the destruction of cartilage matrix components (i.e., PG and type II collagen) and cellular damage after overuse or mechanical injury [5,10]. In parallel with these catabolic events, the synthesis of the matrix components is decreased. Synovial inflammation is directly linked to cartilage degradation, which further up-regulates mediators and effector molecules like IL-8, IL-6, PGE_2, inducible nitric oxide synthase (iNOS) and ROS [10]. In addition, subchondral bone is the site of strong remodeling processes with more bone formation due to increased load resulting in bone sclerosis. All these factors produce the loss of the articular integrity and the loss of joint function [10].

Because it is very difficult to restore the cartilage, there is currently no cure for OA [22]. The only available treatments target symptom reduction (i.e., pain and inflammation), maintenance of joint mobility and limiting the loss of functional capacity. Therefore, decreasing oxidative stress and inflammation production will likely be beneficial to OA management. Recent *in vitro* and preclinical studies suggest the protective roles of dietary polyphenols on progression of OA, in terms of mitigating chondrocyte inflammation and further cartilage damage/destruction, through their ability to directly or indirectly interact with the joint-associated tissues (i.e., articular cartilage, bone or synovium), resulting in the mitigation of joint pain [10,15,23]. This review discusses the potential effects of commonly consumed polyphenols, including curcumin, epigallocatechin gallate (EGCG) and green tea extract, resveratrol, nobiletin and citrus fruits, pomegranate, as well as genistein and soy protein, on joint health based on cell, animal and human studies along with the possible molecular mechanisms.

2. Curcumin

Curcumin (diferuloylmethane) is the major component of tumeric, a yellow spice derived from the plant *Curcuma longa*, and has been reported to be a potent antioxidant and anti-inflammatory agent [24]. The antiosteoarthritic potential of curcumin has been widely studied *in vitro,* mainly in chondrocytes or on articular cartilage explants [25] (Table 1). *In vitro* studies have shown that curcumin decreased catabolic and degradation action of chondrocyte or cartilage explant models when stimulated with inflammatory IL-1β, lipopolysaccharide or TNF-α. Curcumin inhibited the matrix degradation by decreasing the production of MMP-3, -9 and -13 [26–28] via c-Jun-N-terminal kinases (JNK), nuclear factor kappa-B (NF-κB) and the janus kinase-signal transducer and activator of transcription (JAK/STAT) pathway [25]. Moreover, curcumin stimulated matrix synthesis by restoring type II collagen and glycosaminoglycan (GAG) synthesis [27–30].

In addition to its anticatabolic effect, curcumin showed potent anti-inflammatory capabilities by inhibiting key inflammatory mediators (IL-6, IL-8, PGE_2 and NO) and enzymes (COX-2 and iNOS) in both chondrocytes and cartilage explants [31,32]. Curcumin also decreased chondrocyte apoptosis [33] and antagonized inhibitors of cell growth and proapoptotic effects on synovial adherent cells [34]. On the other hand, curcumin inhibited collagenase and stromelysin expression in both synoviocytes and chondrocytes [35]. However, it should be noted that detrimental toxic effects of high doses of curcumin (50 μM) have also been reported in the study of human OA chondrocytes [36]. These findings suggest that dose-seeking studies in animal models of OA are warranted.

Data from several clinical studies are available that examined the effects of curcumin on symptoms in patients with OA (Table 1). In a randomized cross-sectional study, Kuptniratsaikul et al. [37] reported that over a 6-week period, curcumin extract treatment offered benefit similar to that of ibuprofen in pain reduction. In a 3-month registry study ($n=50$), Belcaro et al. [38] reported that Meriva, a proprietary curcumin–phosphatidylcholine phytosome complex, improved symptoms and joint function in OA patients, as assessed by Western Ontario and McMaster Universities (WOMAC) scores and treadmill walking performance. A follow-up 8-month long-term study ($n=100$) by the same team further showed that Meriva improved the clinical end point (assessed by WOMAC, Karnofsky Performance Scale Index and treadmill walking performance) and biochemical inflammatory markers (IL-1β, IL-6, soluble CD40 ligand, soluble vascular cell adhesion molecule-1 and erythrocyte sedimentation rate) in OA patients [39]. Evidence from these clinical studies combined with the results from *in vitro* studies indicate that the beneficial effects of curcumin can be achieved through dietary supplementation; however, optimal doses and the potential for curcumin to enhance matrix synthesis *in vivo* remain to be determined.

3. EGCG and green tea extract

EGCG, a major green tea polyphenol, exhibits antioxidant and anti-inflammatory capabilities. The protective effect of EGCG and green tea extract in the model of inflammatory arthritis is reasonably well reported (Table 2), and most of the data are based on its ability to inhibit the production of key inflammatory mediators (e.g., NO, PGE_2, COX-2, iNOS and IL-8) in various types of cells including human and equine chondrocytes [40–44] and synovial fibroblasts [45]. Such anti-inflammatory effects of EGCG are mediated by inhibited mitogen-activated protein kinase (MAPK), activator protine-1 (AP-1) and JNK activation, which are the critical events in proinflammatory cytokine-induced signaling in chondrocytes that eventually lead to OA [42].

With increasing age, TNF-α and MMP-13 production is induced by advanced glycation end products (AGE), which are responsible for cartilage inflammation and matrix degradation in the development of OA [46]. *In vitro* studies showed that (a) EGCG protects human chondrocytes from the catabolic degradation of cartilage matrix protein by inhibiting the TNF-α, MMP-1, and MMP-13 production [47] and (b) EGCG suppresses IL-1β-induced GAG release from cartilage by inhibiting ADAMTS-1, -4 and -5 [48,49]. These effects appeared to be mediated primarily through the inhibition of NF-κB activation in chondrocytes [46,47].

EGCG not only has anticatabolic effect but also has anabolic effect on OA. EGCG on the anabolic pathways in chondrocytes showed that EGCG attenuates IL-1β-induced suppression of transforming growth

Table 1
Effects of curcumin on OA

First author, year [ref]	Experimental design and treatments	Results
In vitro study		
Liacini, 2003 [26]	Human primary chondrocytes pretreated with curcumin (10 or 15 μM) for 30 min and then co-treated with TNF-α (20 ng/ml) for 24 h Human chondrosarcoma cell line (SW1353) pretreated with curcumin (10 or 15 μM) for 30 min and then co-treated with TNF-α (20 ng/ml) for 24 h	↓ TNF-α-induced MMP-13 expression via JNK and NF-κB signaling pathways
Schulze-Tanzil, 2004 [27]	Human primary articular chondrocytes pretreated with IL-1β (10 ng/mL) for 0, 4, 8, 12 or 24 h and then co-treated with curcumin (50 μM) for 0, 12, 24, 36 or 48 h	↓ IL-1β-induced MMP-3 up-regulation ↓ IL-1β-induced type II collagen synthesis suppression ↓ NF-κB translocation to nucleus
Shakibaei, 2007 [28]	Human primary articular chondrocytes pretreated with IL-1β (10 ng/ml) or TNF-α (10 ng/ml) for 24 h and then co-treated with curcumin (50 μM) and IL-1β (10 ng/ml) for 0, 12, 24, 36 or 48 h	↓ IL-1β- or TNF-α-induced proinflammatory enzymes ↓ IL-1β- or TNF-α-mediated extracellular matrix and integrin degradation ↓ IL-1β-induced-Akt activation, IκβαIκβα phosphorylation, and P65 phosphorylation and translocation of p65 via NF-κB signaling pathway
Shakibaei, 2005 [29]	Human primary articular chondrocytes pretreated with IL-1β (10 ng/ml) for 30 min and then co-treated with curcumin (50 μM) for 5, 15 or 30 min	↓ IL-1β-induced degenerative changes ↓ IL-1β-induced suppression of collagen type II and beta1-integrin synthesis (anticatabolic effect) ↓ IL-1β-induced caspase-3 activation (antiapoptotic effect)
Clutterbuck, 2009 [30]	Equine cartilage explants pretreated with IL-1β (10 or 25 ng/ml) and curcumin (0.1, 0.5, 1, 10 or 100 μmol/L) for 5 days	↓ IL-1β-stimulated GAG release
Mathy-Hartert, 2009 [31]	Human primary articular chondrocytes in alginate beads and human cartilage explants co-treated with IL-1β (10 nM) and curcumin (5–10 μM) for 12 days	↓ NO, PGE_2, IL-6, IL-8 and MMP-3 production in chondrocytes ↓ ^{35}S-GAG release from cartilage explants; therefore, could protect matrix degradation ↔ TIMP-2 and aggrecan productions
Chowdhury, 2008 [32]	Bovine primary articular chondrocytes in agarose co-treated with IL-1β (10 ng/ml) and curcumin (0.01, 0.1, 1, 10 or 100 μg/ml) for 48 h	↓ IL-1β-induced NO and PGE_2 production ↓ IL-1β-induced [^{3}H]-thymidine incorporation
Shakibaei, 2011 [33]	Human primary articular chondrocytes pretreated with curcumin (10 μM) for 0–12 h and then co-treated with IL-1β (10 ng/ml) for 0–48 h	↓ IL-1β-induced apoptosis ↓ IL-1β-induced caspase-3 activation via ERK1/2 signaling pathway
Lev-Ari, 2006 [34]	Human primary osteoarthritic synovial adherent cells from human synovial tissue co-treated with curcumin (10 or 20 μM) and celecoxib (10, 20, 30 or 40 μM) for 72 h	Synergistic effect on the inhibition of osteoarthritic cells via ↓ Cell growth ↑ Induction of apoptosis ↓ COX-2 activity
Jackson, 2006 [35]	Primary chondrocytes isolated from calf cartilage pretreated with curcumin (0.1, 1 or 10 μM) for 6 h and then co-treated with IL-1 (20 ng/ml) for 18 h	↓ IL-1-induced MMP-1, MMP-3 and PG expression
Toegel, 2008 [36]	Immortalized human chondrocytes cell line (C-28/I2) co-treated with IL-1β (10 ng/ml) and curcumin (5 or 50 μM) for 24 or 48 h	At low dose: no effect on aggrecan and type I and II collagen gene expression, proliferation and morphology At high dose: ↓ Cell viability and type I collagen expression ↑ Type II collagen (cartilage major protein) ↑ Matrix degrading enzyme MMP-3 and ADAMTS-4 expression
Csaki, 2009 [56]	Human primary articular chondrocytes pretreated with curcumin (50 μM) for 4 h and then co-treated with IL-1β (10 ng/ml) for 24 h	↓ IL-1β-induced apoptosis (Bcl-2, Bcl-xL) ↓ IL-1β-induced caspase-3 activation ↓ IL-1β-induced NF-κB activation (↓ IκκIκκ activation, IκBα phosphorylation and degradation, and NF-κB nuclear translocation) ↓ NF-κB-regulated gene products involved in inflammation (COX-2, MMP-3, MMP-9, VEGF)
Human study		
Kuptniratsaikul, 2009 [37]	Randomized cross-sectional study Patients with knee OA (n=107) Treatment group (n=52) received *Curcuma domestica* extracts 2 g daily for 6 weeks Comparison group (n=55) received ibuprofen 800 mg daily for 6 weeks	↓ Pain on level walking, time spent on 100-m walk, and time spent on going up and down stairs in both groups
Belcaro, 2010a [38]	Registry study Patients with OA (n=50) received Meriva daily containing 200 mg curcumin for 3 months	↑ WOMAC score ↑ Walking distance in treadmill test ↓ CRP levels
Belcaro, 2010b [39]	Randomized controlled trial Patients with OA (n=100, both genders) Treatment group (n=50) received 1000 mg Meriva daily containing 200 mg curcumin for 8 months Control group (n=50) received none for 8 months	↑ Physical function and quality of life evidence in WOMAC score and Karnofsky Performance Scale Index for OA symptoms ↑ Walking distance in treadmill test ↓ Production of inflammatory markers (IL-1β, sCD40L, sVCAM-1 and ESR)

CRP, c-reactive protein; ERK, extracellular-signal-regulated kinases; ESR, erythrocyte sedimentation rate; sCD40L, soluble CD40 ligand; sVCAM-1, soluble vascular cell adhesion molecule-1; VEGF, vascular endothelial growth factor; ↑, increase; ↓, decrease; ↔, no change.

Table 2
Effects of EGCG and green tea extract on OA

First author, year [ref]	Experimental design and treatments	Results
In vitro study		
Ahmed, 2002 [40]	Human primary chondrocytes co-treated with IL-1β (5 ng/ml) and EGCG (20, 50, 100 or 200 μM) for 24 h	↓ IL-1β-induced iNOS expression and NO production ↓ IL-1β-induced COX-2 expression and PGE_2 production ↓ IL-1β-induced LDH release
Singh, 2002 [41]	Human primary chondrocytes co-treated with IL-1β (2 ng/ml) and EGCG (1, 10, 50 or 100 μM) for 12 or 24 h	↓ IL-1β-induced iNOS expression and NO production ↓ NF-κB activation (↓ IκBα protein degradation in cytoplasm, followed by activation and translocation of NF-κB to nucleus)
Singh, 2003 [42]	Human primary chondrocytes co-treated with IL-1β (2 ng/ml) and EGCG (100 μM) for 30 min	↓ IL-1β-induced phosphorylation of JNK isoforms, accumulation of phospho-c-Jun and DNA binding activity of AP-1 ↔ Activation of extracellular-signal-regulated kinase p44/p42 (ERKp44/p42) or p38-MAPK
Heinecke, 2010 [43]	Equine primary articular cartilage pretreated with EGCG (4, 40 or 400 ng/ml) for 24 h and then co-treated with IL-1β (10 ng/ml) and TNF-α (1 ng/ml) for 24 h	↓ IL-1β- and TNF-α-induced COX-2 expression and PGE_2 production ↓NF-kB translocation to nucleus
Huang, 2010 [45]	Human primary osteoarthritic synovial adherent cells from human synovial tissue pretreated with EGCG (10, 20 or 50 μM) for 12 h and then co-treated with IL-1β for 12 h	↓ IL-1β-induced COX-2 up-regulation ↓ IL-1β-induced PGE_2 and IL-8 production ↓ Phosphorylation of IKKβ
Rasheed, 2009 [46]	Human primary chondrocytes pretreated with EGCG (25, 75 or 150 μM) for 2 h and then co-treated with AGE (600 μg/ml) for 8 h	↓ AGE-stimulated gene expression and production of TNF-α and MMP-13 via ↓p38-MAPK and JNK activation ↓ NF-κB activation (↓IκBα protein degradation in cytoplasm, followed by ↓ activation and translocation of NF-κB to nucleus)
Ahmed, 2004 [47]	Human primary chondrocytes or human cartilage explants co-treated with IL-1β (50 or 10 ng/ml) and EGCG (20, 50, 100 or 200 μM) for 24 or 72 h	↓ IL-1β-induced mRNA and protein expression of MMP-1 and MMP-13 in chondrocytes ↓ IL-1β-induced GAG release from human cartilage explants ↓ Transcription activity of NF-κB and AP-1
Adcocks, 2002 [48]	Bovine cartilage explants co-treated with TNF-α (3 nM) and EGCG (0.2, 2, 20 or 200 μM) for 5 days Human cartilage from OA knee joint co-treated with IL-1β (3 nM), TNF-α (6 nM),and EGCG (20 μM) for 9 days	↓ IL-1β- and TNF-α-induced PG and type II collagen degradation
Andriamanalijaona, 2005 [50]	Bovine primary articular chondrocytes pretreated with EGCG (20 or 50 μM) for 24 h and then co-treated with by IL-1β (10 ng/ml) for 24 h	↓ IL-1β-induced mRNA levels of MMP-1, MMP-3, MMP-13, aggrecanase-1, aggrecanase-2, iNOS, COX-1, COX-2 (anti-inflammatory effect) ↓ IL-1β-induced down-regulation of type II collagen and aggrecan core protein expression ↑ mRNA expression of TGF-β1, TGF-β2, TGF-βR1 and TGF-βII ↓ IL-1β-induced MAPK (Erk1/Erk2, p38 kinase), NF-κB and AP-1 activity
Animal		
Sobhi, 2007 [52]	Intraarticular injection of carrageenan-induced rat arthritis model Treatments including control, arthritic group, arthritic group+1.5% GTE for 3 weeks	Compared to the arthritic group, GTE group: ↓ Lipid peroxides and NO production in plasma ↓ Degenerative and necrotic changes in arthritic joint by a marked reduction in the numbers of inflammatory cells infiltrating the synovial membrane No cartilage and bone erosion

GTE, green tea extract; LDH, lactate dehydrogenase; TGF-βRII, transforming growth factor-β receptor-II.

factor (TGF)-β synthesis and enhances type II collagen and aggrecan core protein synthesis in human articular chondrocytes [50]. Furthermore, new target proteins of EGCG for the protection of the cartilage and chondrocytes were reported from the study of protein array data (80 proteins), which suggested that proteins having chondrocyte protective effects would be potential candidates for OA treatment [51].

In a carrageenan-induced arthritic animal model, Sobhi et al. [52] reported that green tea extract suppressed lipid peroxides and NO in the plasma and improved the arthritic degenerative joint, as shown in a marked reduction in the numbers of the inflammatory cells infiltrating the synovial membrane compared to the untreated animals. Haqqi et al. also reported that green tea polyphenols provided through drinking water prevented collagen-induced arthritis in mice, as evidenced by a marked reduction of collagen-induced COX-2 and TNF-α in arthritic joints [53]. However, it should be noted that there is a concern with the applicability of the animal models used in these studies to the etiology of OA.

In summary, the existing evidence from both *in vitro* and *in vivo* studies suggests that EGCG could reduce synovial hyperplasia, cartilage degradation and bone resorption by modulating multiple targets in joints during the development of OA.

4. Resveratrol

Resveratrol is a natural phytoalexin (polyphenolic compound) that is found in the grape skin, berries and peanuts [54]. Resveratrol may have antiosteoarthritic effects due to its antiapoptotic, anti-inflammatory and antioxidant properties (Table 3).

Table 3
Effects of resveratrol on OA

First author, year [ref]	Experimental design and treatments	Results
In vitro study		
Shakibaei, 2011 [33]	Human primary articular chondrocytes pretreated with resveratrol (10 μM) 4 h and then co-treated with resveratrol (10 μM) and IL-1β (10 ng/ml) for 1, 12, 24 or 48 h	↓ IL-1β-induced apoptosis ↓ IL-1β-induced caspase-3 activation via ERK1/2 signaling pathway
Dave, 2008 [55]	Human primary chondrocytes, human cartilage explants or normal bovine chondrocytes pretreated with resveratrol (1, 5 or 10 μM) for 1 h and then co-treated with IL-1β (10 ng/ml) for 24 h	↓ IL-1β-induced COX-2 expression/activity and PGE_2 and LTB_4 production in chondrocytes (anti-inflammatory effect) ↓ IL-1β-induced mitochondrial dysfunction, ATP depletion, expression of apoptotic markers and DNA fragmentation in chondrocytes (antiapoptotic effect) ↓ IL-1β-induced apoptosis of chondrocytes ↓ Pro-MMP-13 production in cartilage explants ↓ PG degradation from cartilage explants
Csaki, 2009 [56]	Human primary articular chondrocytes co-treated with IL-1β (10 ng/ml) and resveratrol (50 μM) for 1, 12, 24, 36 or 48 h	↓ IL-1β-induced apoptosis (Bcl-2, Bcl-xL) ↓ IL-1β-induced caspase-3 activation ↓ IL-1β-induced NF-κB activation (↓ Iκκ activation, IκBα phosphorylation and degradation, and NF-κB nuclear translocation) ↓ NF-κB-regulated gene products involved in inflammation (COX-2, MMP-3, MMP-9, VEGF)
Shakibaei, 2008 [57]	Human primary articular chondrocytes pretreated with resveratrol (100 μM) for 4 h and then co-treated with IL-1β (10 ng/ml) for 1, 2, 4, 8, 12, 20 or 24 h	↓ IL-1β-induced IκBα degradation and nuclear translocation of NF-κB ↓ IL-1β-induced MMP-3, MMP-9 and COX-2 production ↓ IL-1β-induced NF-κB-dependent proinflammatory and matrix degradation gene products ↓ IL-1β-induced apoptosis, caspase-3 activation and PARP cleavage
Csaki, 2008 [58]	Human primary articular chondrocytes co-treated with IL-1β (10 ng/ml) and resveratrol (0.1, 1, 10, 50 or 100 μM) for 1, 12, 24, 36 or 48 h	↓ IL-1β-induced degradation of mitochondria and apoptosis ↓ IL-1β-induced caspase-3 and DNA fragmentation ↓ IL-1β-induced production of ROS and tumor suppressor gene protein p53
Shakibaei, 2007 [59]	Human primary articular chondrocytes pretreated with IL-1β (10 ng/ml) for 1, 12 or 24 h and then co-treated with IL-1β (10 ng/ml) and resveratrol (100 μM) for 1, 12 or 24 h	↓ IL-1β-induced inhibition of extracellular matrix (collagen type II) and signaling proteins (integrin-β1) synthesis ↓ IL-1β-induced caspase-3 activation and PARP cleavage
Lei, 2008 [67]	MSC-derived chondrocytes cultured on CGS co-treated with IL-1β (10 ng/ml) and resveratrol (100 μM) for 24 h	↓ IL-1β-induced translocation of NF-κB ↓ IL-1β-induced MMP-13 expression ↓ IL-1β-induced down-regulation of type II collagen and aggrecan
Liu, 2010 [68]	Porcine primary chondrocytes pretreated with resveratrol (25, 50, 75 or 100 μM) for 24 h and then co-treated with AGEs (100 μg/ml) for 24 h Porcine cartilage explants pretreated with resveratrol (50 or 100 μM) for 24 h and then co-treated with AGEs (100 μg/ml) for 72 h	↓ AGE-induced expression of iNOS and COX-2 and production of NO and PGE_2 in chondrocytes ↓ AGE-induced IKK-IκBα-NF-κB signaling in chondrocytes ↓ AGE-induced expression and activity of MMP-13 in chondrocytes ↓ AGE-mediated degradation of type II collagen, PG and aggrecan in cartilage explants
Lei, 2012 [69]	Rat primary articular chondrocytes pretreated with resveratrol (5, 10 or 20 μM) for 1 h and then co-treated with IL-1β (10 ng/ml) for 8 h	↓ IL-1β-induced iNOS expression and NO production ↓ IL-1β-induced activation of NF-κB pathway by activating SIRT1
Animal		
Elmali, 2005 [70]	Rabbits underwent unilateral anterior cruciate ligament transaction (surgical OA arthritic model) Groups including control group (vehicle) or treatment group receiving injection of resveratrol (10 μmol/kg) in the knees once daily for 2 weeks	↓ Cartilage tissue destruction ↓ Loss of matrix PG content in cartilage ↔ Synovial inflammation
Wang, 2011 [71]	Rabbits underwent unilateral anterior cruciate ligament transaction (surgical OA arthritic model) Groups including normal control, OA model control, OA model+resveratrol (50 μmol/kg), OA model+resveratrol (20 μmol/kg) or OA model+resveratrol (10 μmol/kg) for 2 weeks	↓ Cartilage tissue destruction ↓ Loss of matrix PG content in cartilage ↓ Chondrocyte apoptosis ↓ NO level in synovial fluid

CGS, chitosan-gelatin scaffolds; LTB_4, leukotriene B_4; MSC, mesenchymal stem cells.

Studies of resveratrol's potential OA-protective effects have demonstrated its ability to inhibit chondrocyte apoptosis induced by IL-1β-stimulated inflammation in human articular chondrocytes [55–57]. Such antiapoptotic effects by resveratrol were mediated by (a) decreased activity of caspase-3 and decreased subsequent cleavage of the DNA repair enzyme, poly (ACP-ribose) polymerase (PARP) [58,59] or (b) suppressed mitochondrial ROS and p53 production, which in turn activates caspase-3 activity and cellar apoptosis [33,58]. In addition, resveratrol also blocks IL-1β- and TNF-α-induced activation of NF-κB [60,61], which is known to regulate NO-, IL-1β- and IL-17-induced chondrocyte apoptosis [62–66].

In vitro studies also show that resveratrol protects against OA-associated changes by decreasing the expression of vascular endothelial growth factor and COX-2 as well as by down-regulating the activity of MMPs involved in matrix degradation [57]. Resveratrol inhibited the degradation of cartilage matrix by protecting the major cartilage matrix proteins, PG, collagen type II and aggrecan, from the matrix degrading enzyme (MMPs) or inflammatory stimuli (i.e., iNOS, COX2) [67–69].

Table 4
Effect of nobiletin and citrus fruits on OA

First author, year [ref]	Experimental design and treatments	Results
In vitro study		
Imada, 2008 [77]	Normal human synovial fibroblasts co-treated with IL-1β (10 ng/ml) and nobiletin (16, 32 or 64 μM) for 24 h	↓ IL-1β-mediated ADAMTS-4 and ADAMTS-5 mRNA expression
Lin, 2003 [78]	Normal human synovial fibroblasts co-treated with IL-1α (1 ng/ml) and nobiletin (4, 8, 16, 32 or 64 μM) for 24 h	↓ IL-1α-induced PGE_2 production ↓ IL-1α-induced COX-2 but not COX-1 mRNA expression ↓ IL-1α-induced gene expression and production of pro-MMP-1 and pro-MMP-3 ↑ Production of TIMP-1
Ishiwa, 2000 [79]	Rabbit synovial fibroblasts co-treated with IL-1α (1 ng/ml) and nobiletin (4, 8, 16, 32 or 64 μM) for 24 h	↓ IL-1β-induced proMMP-9 mRNA expression and production ↓ IL-1β-induced PGE_2 production ↓ Proliferation of synovial fibroblasts in growth phase which causes inflammatory actions in growth phase
Animal		
Imada, 2008 [77]	After initial collagen immunization in CIA mice, nobiletin (15, 30 or 60 mg/kg) or vehicle were intraperitoneally administered daily from day 21 to 41	↓ ADAMTS-4 and -5 mRNA expression in joint tissues ↓ Aggrecanase-mediated degradation of aggrecan in cartilage ↓ Hind paws swelling and incidence of arthritis ↓ Severity of inflammation, pannus formation, and cartilage and bone damage
Human		
Oben, 2008 and 2009 [83,84]	Cross-sectional study Patients with knee OA (n=80 with n=45 completed) Treatments: Group 1: overweight subjects with placebo (740 mg) Group 2: overweight subjects with NP 06-1 (combination of 2 botanical extracts; *P. amurense* bark and *C. sinensis* peel) (740 mg) Group 3: normal-weight subjects with placebo Group 4: normal-weight subjects with NP 06-1	↓ Body weight and blood pressure ↓ Joint pain (assessed by Lequesne Algofunctional Index) ↓ CRP levels

CIA, collagen-induced arthritic.

Two *in vivo* studies have examined the effects of resveratrol administered through intraarticular injections on OA. In the first study, Elmali et al. [70] reported that 2 weeks of resveratrol supplementation resulted in a significant reduction in cartilage destruction and PG loss in rabbits receiving anterior cruciate ligament transection. Only a trend (P=.057) toward reduced inflammation within the synovium as indicated by the thickening of the synovial lining layer and infiltrating cells was reported, which may suggest that resveratrol benefits were mediated through other mechanisms. A subsequent study by Wang et al. [71] investigated the effects of 2 weeks of resveratrol injections on histological changes within cartilage, chondrocyte apoptosis and NO production of synovial fluid in a joint destabilization model involving the transection of both the anterior and posterior cruciate ligaments. They also reported reduced cartilage destruction and PG loss based on histological examination. These protective effects of resveratrol resulted in a decrease in arthritis-induced chondrocyte apoptosis and synovial NO content. It is important to note that the efficacy of resveratrol in these studies was observed through direct exposure of resveratrol to the joint instead of dietary supplementation. It is not clear whether the same benefits would be provided through oral supplementation.

5. Nobiletin and citrus fruits

Nobiletin (5,6,7,8,30,40-hexamethoxyflavone), a citrus polymethoxylated flavonoid, is present in orange and a number of citrus fruits. It has been shown to have anti-inflammatory and antitumor effects (i.e., cell proliferation, invasion and metastasis) *in vitro* and *in vivo* [72,73]. Most of the antiosteoarthritic potentials of nobiletin have been investigated using *in vitro* models of synovial fibroblasts and articular chondrocytes (Table 4).

Early events in cartilage destruction associated with OA involve the loss of the large PG, aggrecan, by the proteolytic activity of ADAMTS-4 and ADAMTS-5 [74–76]. Nobiletin (16–64 μM) inhibited cartilage degradation by interfering with the production and activity of the enzymes involved in cartilage destruction, such as ADAMTS-4 and ADAMTS-5, in cultured human synovial fibroblasts [77]. Nobiletin prevented matrix degradation of the articular cartilage as well as pannus formation due to its anti-inflammatory effect. Nobiletin suppressed the production of matrix catabolic factors, including the catabolic factor as promatrix metalloproteinase (proMMP-9/progelatinase B) in rabbit synovial fibroblasts and PGE_2 in rabbit articular chondrocytes. Nobiletin also protected the matrix construction by activating the MMP inhibitor [tissue inhibitor of metalloproteinase-1 (TIMP-1)] in human synovial fibroblasts, macrophages in mouse [78] and articular chondrocytes in rabbit [79].

In both OA and rheumatoid arthritis animal models, by-products of aggrecan degradation are increased within the synovial fluid [75]. Imada et al. [77] showed that nobiletin (15, 30 or 60 mg/kg) administered by daily intraperitoneal injection (21 days) to collagen-induced arthritis mice interfered with ADAMTS-4 and -5 expression in cartilage and prevented cartilage destruction. Histological evaluation demonstrated that with a higher dose of nobiletin, inflammation, pannus, cartilage damage and underlying bone damage were decreased. Although the collagen-induced arthritis model is considered a model of rheumatoid arthritis, nobiletin's suppression of ADAMTS-4 and ADAMTS-5 suggests possible benefit of this citrus flavonoid to OA as well.

Citrus sinensis (orange) peel extracts contain bioflavonoids, including polymethoxylated flavones (PMFs). The latter compounds are known to be anti-inflammatory and to have antioxidant and hypolipidemic effects [80–84]. Oben et al. [83,84] studied the effects of NP06-1 (Flavoxine/Citrofen, Next Pharmaceuticals, Inc., Salinas, CA, USA), a blend of extracts of *Phellodendron amurense* tree bark and *C. sinensis* (orange) peel standardized to berberine and PMFs, on the management of joint pain and mobility in patients with knee OA. It was reported that compared to the placebo, NP06-1 supplementation for 8 weeks resulted in significant loss in body weight and

Table 5
Effects of pomegranate on OA

First author, year [ref]	Experimental design and treatments	Results
In vitro study		
Ahmed, 2005 [24]	Human primary chondrocytes co-treated with IL-1β (5 μg/L) and PFE (6.25, 12.5, 25 or 50 mg/L) for 24 h	↓ IL-1β-induced PG release from OA cartilage ↓ IL-1β-induced mRNA and protein expression of MMP-1, MMP-3 and MMP-13 ↓ IL-1β-induced phosphorylation of ERK, JNK and p38-MAPK ↓ IL-1β-induced phosphorylation of IκBα ↓ IL-1β-induced DNA binding activity of NF-κB
Rasheed, 2010 [90]	Human primary chondrocytes pretreated with PFE (6.25, 12.5, 25 or 50 μg/ml) for 2 h and then co-treated with IL-1β (10 ng/ml) for 3 min	↓ IL-1β-induced activation of MKK3 and MKK6 ↓ IL-1β-induced activation of p38α-MAPK isoform ↓ IL-1β-induced activation of transcription factor RUNX-2
Animal study		
Shukla, 2008 [89]	Rabbit were orally administrated with vehicle or 10 ml PFE (34 mg/kg, equivalent to 175 ml of pomegranate juice on the basis of the phenolics content) Rabbit primary chondrocytes treated with 200 μl of control or experimental plasma samples (orally receiving PFE) for 1 h and then co-treated with IL-1β (5 ng/ml) for 24 h	In plasma: ↓ IL-1β-induced both COX-1 and COX-2 enzyme activity *ex vivo* in plasma of rabbits 2 h after administration of PFE In chondrocytes: ↓ IL-1β-induced PGE_2 and NO production *ex vivo* in chondrocytes
Hadipour-Jahromy, 2010 [92]	Male mice MIA-induced OA of knee joint model Treatments including control (water) group or PJ (4, 10 or 20 ml/kg daily) orally for 14 days	↓ Disorganization of chondrocytes, erosion and fibrillation of cartilage surface, subchondral bone exposure and loss of PG in cartilage (chondroprotective effect) No cell proliferation or inflammatory cells detected in synovial fluid (anti-inflammatory effect)

MIA, monosodium iodoacetate; PFE, pomegranate fruit extract; PJ, pomegranate juice; RUNX-2, runt-related transcription factor-2.

improvement in joint pain (as assessed by Lequesne Algofunctional Index) along with a reduction in inflammation (i.e., decreased C-reactive protein levels) in overweight patients with knee OA [83,84]. The authors concluded that NP 06-1 may benefit patients with knee OA through anti-inflammation and loss of body weight. In *in vivo* and *in vitro* studies, PMFs regulated levels of adipocytokines by way of suppressing TNF-α, interferon-γ, IL-1β and IL-6 expression [85]. PMFs also suppressed TNF-α expression by monocytes, perhaps due to inhibition of phosphodiesterase activity [86]. Based on these studies, nobiletin and other polyphenolic compounds in citrus fruit may hold promise as therapeutic options for OA.

6. Pomegranate

Pomegranate (*Punica granatum* L, Punicaceae) is an edible pinky-reddish fruit that is native to Persia but grown and consumed around the world. Pomegranates are a good source of vitamin C, providing between 10% and 20% of the recommended daily requirement per cup. The potent antioxidant properties of pomegranates have been attributed to their high content of soluble polyphenols, including the hydrolyzable tannin and punicalagin [87]. In addition, the pomegranate's yield of alkaloids in the form of tannates varies from approximately 0.5% tannin from the root and stem barks to 28% tannin in the fruit's highly astringent pericarp [88]. Pomegranate is rich in anthocyanins, a polyphenolic compound that possesses antioxidant and anti-inflammatory capabilities [24]. Table 5 summarizes the effects of pomegranate relevant to OA.

The cartilage protective effects of pomegranate are characterized by its ability to inhibit the activity and action of matrix degradation enzyme MMPs and NF-κB activity stimulated by inflammatory condition [89]. Pomegranate demonstrated anti-inflammatory action via inhibiting the activity of the major inflammatory enzyme (COX-2) and the production of its inflammatory mediator product PGE_2 [90]. Pomegranate extracts also prevented the activation of molecules [MAPK kinase-3 (MKK-3), p38-MAPK] which are the molecules of the stimulatory pathway for inducing OA in chondrocytes [91].

Prodelphinidin is a condensed polymeric tannin composed of gallocatechin that can be found in the pomegranate, green tea leaves, etc. In human chondrocytes, prodelphinidin increased the synthesis of cartilage matrix major proteins, PGs and type II collagen, and inhibited PGE_2 synthesis by down-regulating COX-2 action [91]. These *in vitro* studies have provided support for additional preclinical assessment of prodelphinidin in the treatment of OA.

To date, only two animal studies have been reported in the literature that tested the efficacy of pomegranate in the treatment of OA (Table 5). Hadipour-Jahromy and Mozaffari-Kermani [92] utilized the monoiodoacetate OA model which induces articular cartilage degradation and mimics some aspects of OA observed in humans. In this model, monosodium iodoacetate is injected directly into the joints of mice and acts to inhibit 3-glyceraldehyde-3-phosphate dehydrogenase activity in chondrocytes, which interrupts glycolysis and ultimately leads to cell death and cartilage degradation. Pomegranate juice (0, 4, 10 or 20 ml/kg administered by oral gavage for 2 weeks) significantly reduced chondrocyte damage and PG loss, especially in the groups receiving the higher doses. No synovial cell proliferation or inflammatory cells were observed with any dose. This study provides some *in vivo* evidence that pomegranate juice may improve the joint pathology in OA.

Although pomegranate fruit extract has shown to inhibit cartilage degradation in OA by reducing expression of the inflammatory chemical IL-1β [24] *in vitro* and to suppress inflammation and joint damage in rheumatoid arthritis in animals [89,92], to date, there are no human studies related to its efficacy reported in the literature.

7. Genistein and soy protein

Genistein, an isoflavone found in soybeans and soy products, acts as a phytoestrogen. The suggested anti-OA activity of phytoestrogens is due to the relationship between OA and an altered estrogen metabolism [93]. Phytoestrogens, as their name suggests, have some estrogen activity and may ameliorate menopausal symptoms as well as the symptoms of OA [93]. Cartilage is an estrogen receptor positive tissue, the expression of estrogen receptor (beta) is increased after menopause, and menopause can increase the incidence of OA [94,95]. Therefore, it can be hypothesized that estrogen receptor modulators, such as genistein, can modulate estrogen receptor expression and improve cartilage health. Hence, phytoestrogens can be a candidate

Table 6
Effects of genistein and soy protein on OA

First author, year [ref]	Experimental design and treatments	Results
In vitro study		
Hooshmand, 2007 [96]	Human normal chondrocytes pretreated with genistein (0, 25, 50, 100 or 200 μM) for 1 h and then co-treated with LPS (1 μg/ml) for 24 h	↓ LPS-stimulated COX-2 protein levels ↓ LPS-induced NO production ↔ YKL-40 (serum levels of glycoprotein 39)
Claassen, 2008 [93]	Bovine primary articular chondrocytes treated with daidzein or genistein (10^{-4}–10^{-11} M) for up to 7 days	↑ Insulin-stimulated sulfate intake which increases articular cartilage matrix component, GAG
Cheng, 2010 [98]	Human chondrocytes cell line (CHON-002) pretreated phytoestrogen bavachin (1, 2.5, 5, 10 or 20 μM) for 24 h followed by IL-1β (5 ng/ml) for 24 h	↓ IL-1β-induced NF-κB action (↓ IκBα degradation in cytoplasm, followed by ↓ activation and translocation of NF-κB to nucleus) ↓ IL-1β-induced chemokine production
Animals		
Ham, 2002 and 2004 [99,100]	Ovariectomized cynomolgus monkeys received ERT (conjugated equine estrogens), SPE (SUPRO 670-HG soy protein isolate, containing 1.105 mg of genistein, 0.365 mg of daidzein and 0.08 mg of glycitein per gram of soy protein isolate) or no treatment (control) for 3 years	↔ Cartilage or bone lesions of OA ↔ IGFBP-2, IGFBP-3, collagen or PG levels
Human		
Arjmandi, 2004 [101]	Randomized controlled trial (n=135 including 64 men and 71 women) Group 1 received 40 g soy isolate group for 3 months Group 2 received 40 g milk-based protein group for 3 months	In men: ↑ OA-associated symptoms (range of motion and several factors associated with pain and quality of life) ↑ Serum IGF-I levels ↓ Serum YKL-40 levels (glycoprotein 39)

ERT, estrogen replacement therapy; IGFBP, insulin-like growth factor binding protein; LPS, lipopolysaccharide; SPE, soy phytoestrogen.

for OA protection [96,97]. Table 6 summarizes the effects of genistein and soy protein on OA.

So far, studies on the effects of phytoestrogens, including genistein and daidzein, are very limited. Nevertheless, some positive effects have been reported. Genistein was shown to suppress the production of COX-2 and NO in primary human chondrocytes [96]. Genistein also increased GAG synthesis by increasing sulfate content within the treatment range of 10^{-9}–10^{-5} M concentration [93], but had negative effects at higher doses (i.e., 10^{-5}–10^{-4} M). Other phytoestrogens, such as bavachin extracted from the seeds of *Psoralea corylifolia* L, showed protection of OA in both human chondrocytes and the chondrocytic cell line CHON-002 by decreasing inflammatory cytokine IL-1β-induced activation of NF-κB signaling pathway [98].

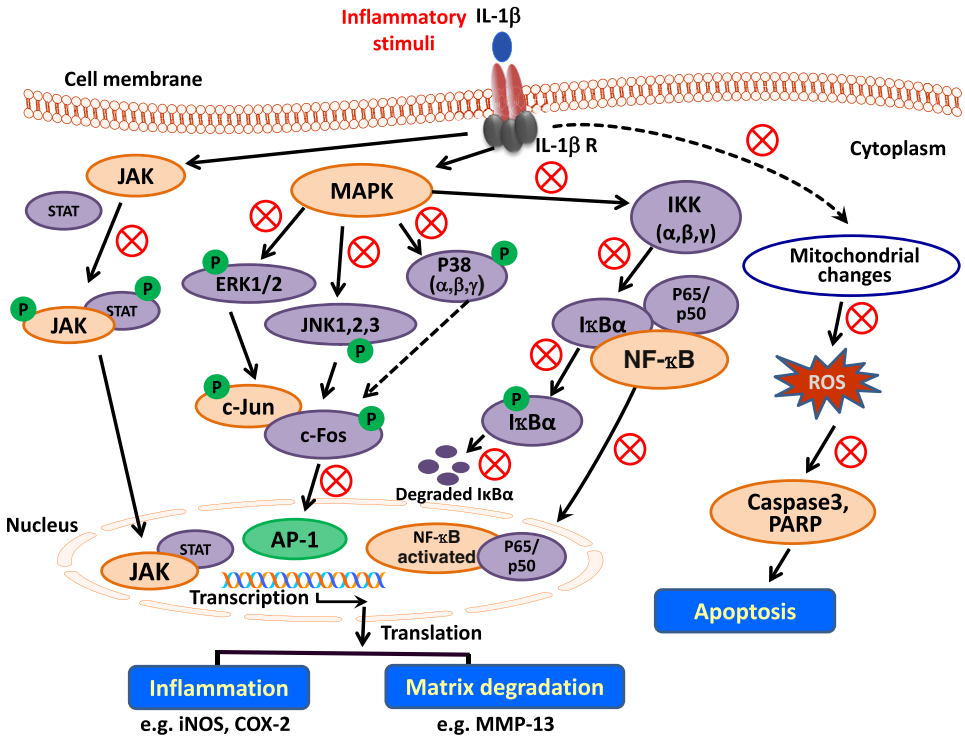

Fig. 1. The molecular mechanisms of dietary polyphenols' effects on cartilage chondrocytes. Dietary polyphenols (DP) mitigate inflammation and degeneration of joint by modulating STAT, MAPK, AP-1 and NF-κB signaling pathways. Dietary polyphenols also inhibit apoptosis of chondrocytes. The activation of STAT, MAPK, AP-1 and NF-κB signalings leads to the generation of iNOS, COX-2 and MMP-13 that causes the degradation of cartilage matrix. With the activation of these critical pathways by inflammatory stimuli (IL-1β), many relevant events were blocked by the supplementation of dietary polyphenols as indicated by ⊗.

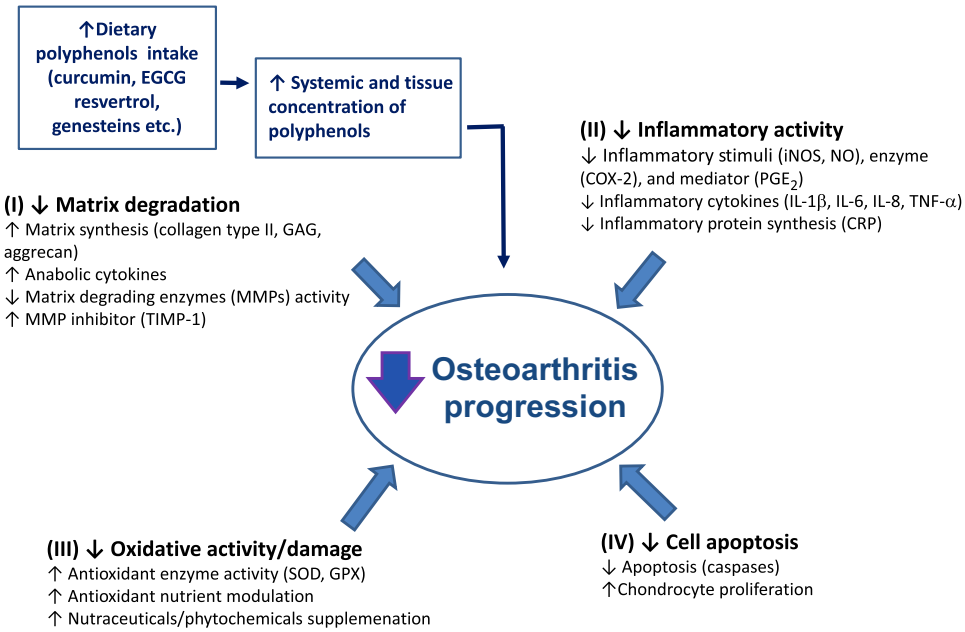

Fig. 2. The potential therapeutic approach to inhibit the progression of OA by dietary polyphenols. ↑: increase. ↓: decrease.

In a well-characterized monkey model of naturally occurring OA, Ham et al. reported that long-term soy phytoestrogen supplementation did not have a significant impact on the articular cartilage lesions of osteoarthritic knee [99]. Soy phytoestrogens also had no significant effect on the levels of any of the cartilage components in this monkey model [100].

In one human study, Arjmandi et al. [101] reported that compared to milk-based protein, 3 months of soy protein supplementation to individuals (64 men and 71 women) with OA (a) improved OA-associated symptoms, such as range of motion and factors associated with pain and quality of life, and (b) increased serum IGF-I and reduced serum glycoprotein 39, biochemical markers of cartilage metabolism. However, such beneficial effects were only observed in men, not in women. Further clinical studies to evaluate the long-term effects on both men and women are warranted.

8. Summary and future research

OA is associated with an imbalance between the catabolic activity and anabolic activity within the cartilage matrix and bony structures of joints. Scientific evidence suggests that dietary polyphenols benefit the management of inflammatory arthritis and may therefore benefit OA. The antiosteoarthritic effects seem to be mediated via the down-regulation of inflammatory cytokines, ant-oxidant or anti-inflammation pathway and their signaling mechanism. Fig. 1 illustrates the possible molecular mechanisms (anti-inflammatory, antioxidant and anticatabolic activities) of dietary polyphenols' effects on the development of OA. It is noted that Fig. 1 is based on the mechanisms reported in the literature with various dietary polyphenols, and not all of these mechanisms apply to every dietary polyphenol.

The results of *in vitro* and preclinical work are preliminary; nevertheless, they suggest the promising potential of dietary polyphenols in the amelioration of the associated symptoms of OA. Based on review of the current literature, the therapeutic potential of dietary polyphenols to manage OA is illustrated in Fig. 2. At present, there is no effective treatment to cure OA, and the current therapy can only alleviate the symptoms. Currently, there is no very effective nutritional supplement to counteract OA, even glucosamine [102].

The current review reveals that more *in vivo* studies are required to understand the efficacy, safety and targets of dietary polyphenols using OA animal models. Given the significant content of dietary polyphenols in typical human diet and the potential of dietary supplements, more well-designed human clinical trials are mandatory to evaluate the effects of dietary polyphenols on OA in terms of functional, symptomic, structural and biochemical outcomes. Dietary polyphenols may also be tested as an adjunctive treatment in combination with already known pharmaceutical drugs for OA. Such approach may enhance the antiosteoarthritic efficacy of these drugs, lower the dose or extend the interval between treatment episodes of the drugs, thus reducing the risk of adverse effects caused by the long-term toxicity of these drugs such as nonsteroid anti-inflammatory drugs.

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